No. 03-1237

In the Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF AMICUS CURIAE VACCINEX, INC. IN SUPPORT OF RESPONDENTS

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March 22, 2005

QUESTION PRESENTED

Whether the "safe harbor" provision of section 271(e)(1) of the Patent Act extends to acts of infringement arising from use of "research tools" to identify, characterize, or optimize a substance that may subsequently become the subject of an application to the Federal Drug Administration.

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Interest of the *Amicus*

This brief is filed with the consent of the parties[1] on behalf of Vaccinex, Inc., a biotechnology company engaged in the discovery of human antibodies and their subsequent development into novel therapeutic drugs to treat a variety of diseases. Vaccinex possesses proprietary antibody discovery technology for the direct selection of high affinity, fully human monoclonal antibodies from libraries expressed in mammalian cells. Vaccinex is commercializing this

[1] The parties' letters of consent have been filed with the Clerk in compliance with Rule 37.3.(a). This brief was not authored in whole or in part by counsel for any party.

technology by discovering antibodies for the development of their own in-house pipeline of therapeutic antibodies, for antibody co-development partners, and for client companies needing fee-based research services. Vaccinex provides research tools that enable it and other entities to undertake significant drug research and development.

This brief seeks to advise the Court of the use of research tools in the drug development process, the significance of those tools as essential to modern drug research, and the fact that when the tools are used to identify, characterize, or optimize candidates for possible submission to the FDA the use is not "solely [and] reasonably" related to submission of data to the FDA.

The Court of Appeals decision correctly discussed the impact of its decision on the use of patented research tools, insofar as the record before it defined the relevant facts. That decision was based on the fact that the FDA application that forms a critical basis for the positions Merck and the United States are taking in this Court was not in the record on appeal. The briefs now before the Court, however, raise new facts that might distort the analysis of the critical issue insofar as research tool patents are concerned.

We believe this case may be inadequate to decide the scope of the exemption with respect to research tools. Because the record before the Court of Appeals differed substantially from the information placed before this Court, the decision below should be affirmed on the basis of the record that was before that court, or the Court should dismiss the writ as improvidently granted.

Summary of Argument

The discovery and development of research tools have been the cornerstone of the biotechnology industry. A research tool may be generally defined as "a technology that

is used by pharmaceutical and biotechnology companies to find, refine, or otherwise design and identify a potential product or properties of a potential drug product."[2] Examples of research tools include conventional tools such as centrifuges, pipettes, and test tubes, but also include highly technical discoveries such as "high-throughput screening technologies, micro-array-type technologies, genomic databases, and computer modeling programs."[3] These tool technologies have changed the face of pharmaceutical research, allowing innovative new drugs to be discovered and developed, in a fraction of the time that might have been required otherwise. Development of innovative new research tools is an expensive undertaking. Accordingly, biotechnology companies with a tool technology platform have relied on patent protection to obtain sufficient capital.

Research tools might be used throughout the course of drug development, and indeed, certain tools may be utilized solely during the preparation of information for submission to the FDA. But the most important utilization of highly technical research tools is during the identification, characterization and optimization of potential new drugs — well before the point at which a drug candidate is entered into preclinical or clinical studies.

In the district court, the parties were precluded from introducing the evidence that forms the critical factual basis for Merck's assertion that the patented invention was used to generate information that was in fact submitted to the FDA. The Investigational New Drug application that Merck relies

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[2] Fed. Trade Comm'n, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*, ch. 3, at 18 (2003), *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf (last visited March 21, 2005).

[3] *Id.*, ch. 3, at 18-19.

on was not submitted to the FDA until after discovery closed. (Pet. Br. at 18.)[4] The research that produced the data submitted to the FDA was not introduced after the trial court ruled that the parties could not use it because Merck failed to produce the material in response to a proper document request. (Jan. 5, 2000 Order of the District Court, Docket # 844; J.A. 9) The Court of Appeals for the Federal Circuit, based on the record before it, understandably concluded that the infringing "experiments did not supply information for submission to the United States Food and Drug Administration (FDA)." (P.A. at 11a; 331 F.2d at 865.) Merck admitted in the trial court that it did "not claim that all of [the challenged] activities are exempt under Section 271." (Docket # 930 at 6.)

The jury instruction on the FDA exemption was essentially the instruction that Merck requested. The jury was specifically asked whether Merck had "met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA exemption" and answered "No." (J.A. 63a.) Merck's post-verdict Motion for Judgment as a Matter of Law was denied and the trial judge specifically noted that Merck's own witness "admitted that Merck's infringing activity was not necessary in order to carry out any preclinical work required for Merck's RGD peptides." (Docket # 1133 at 2.) The trial judge listed numerous other parts of the evidence that supported the jury's verdict. (*Id.*) Because the NCI IND application and associated experimental data was not in the record, the Court of Appeals' conclusion that the patented invention had been used to identify, characterize, or optimize candidates for potential submission to the FDA, and not to obtain

[4] This brief uses the same abbreviations as those defined in footnote 1 of the Brief for the Petitioner, with the addition of the abbreviation "Pet. Br." for the Brief For Petitioner filed February 15, 2005.

information that was in fact submitted to the FDA, was fully supported.

Based on evidence that was not in the record but has been described in the briefs Merck and the Solicitor General have filed, it now appears that the patented invention may have actually been used, at least in part, to generate information that was submitted after the close of discovery to the FDA by the National Cancer Institute as part of an IND application. That significant addition to the facts raises a substantial issue for the Court: should this Court decide the case on the basis of the record as developed in the district court, or on the basis of the record as supplemented here by information the district court specifically precluded? Vaccinex submits that any opinion from this Court should either affirm that the "safe harbor" exemption does not extend to use of patented research tools to identify, characterize, or optimize candidates for potential subsequent submission to the FDA or dismiss the writ as improvidently granted.

Argument

I. Research Tools Covered by Valid Patents Are Essential to Development of New Drugs and Loss of Patent Protection Could Preclude Development of Those Tools

Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 668-74 (1990), discusses the complementary relationship between § 201 of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585, (1984), which provided patent term extension for patents to drugs, medical devices, food additives or color additives which experienced delays in regulatory approval, and § 202 of the Act, which established the § 271(e)(1) infringement

exemption. Acknowledging the intended balance of rights provided by two provisions, Justice Scalia wrote that under the Court's statutory construction "there may be some relatively rare situations in which a patentee will obtain the advantage of the § 201 extension but not suffer the disadvantage of the § 202 noninfringement provision, and others in which he will suffer the disadvantage without the benefit." *Eli Lilly*, 496 U.S. at 671-72.

Vaccinex respectfully submits that patented research tools represent a situation where a patentee could suffer the disadvantages of § 202, with none of the advantages of § 201. Indeed, many research tool patentees would be threatened with losing all rights under the Patent Act if the decision of the Court of Appeals were reversed.

A. Patented Research Tools Are Used to Identify, Characterize and Optimize Candidates for Possible Subsequent Submission to the FDA

Discovery and development of research tools is a complex and expensive undertaking. Entire sub-industries in biotechnology[5] have been formed that are comprised of companies having a research tool (rather than a drug product) as their platform technology. These "research tool" companies have in no small part fueled the identification and development of promising new drugs.

For example, the identification, characterization, and optimization of therapeutic monoclonal antibodies have relied heavily on research tools. Monoclonal antibody technology is one of the fastest growing areas in drug development. While the market for therapeutic monoclonal antibodies is relatively young, 17 therapeutic monoclonal

[5] *E.g.*, genomics, proteomics, nucleic acid amplification, antibody engineering, transgenics, bioinformatics, etc.

antibody products have entered the market.[6] Of these, two have already exceeded one billion in annual sales.[7] In addition, at least 100 other monoclonal antibodies have entered clinical trials.[8] Sales of therapeutic antibodies are anticipated to grow from $5 billion in 2002 to $17 billion in 2008.[9] Based on this dramatic growth and market success, the development of therapeutic antibodies has become a major focus of biotechnology and pharmaceutical companies. As a panelist before the Federal Trade Commission testified, "research tools have led to a considerable reduction in the cost and time required for the targeting of therapeutic antibodies during the initial stages of new drug research."[10]

Mouse monoclonal antibodies, produced by hybridoma cells, first appeared in the mid-1970s to great fanfare. These antibodies had limited use as pharmaceuticals, because the human immune system would reject the antibodies as foreign. In response, a number of research tool technologies for making these antibodies more "human" were developed. Subsequently, tools were developed to identify fully human antibodies and to improve

[6] *See* U.S. Food & Drug Admin., *Therapeutic Biological Products Approvals*, *at* http://www.fda.gov/cder/biologics/biologics_table.htm (last visited March 21, 2005).

[7] See Genetech, Inc. "Historical Product Sales" data for Rituxan found at http://www.gene.com/gene/ir/financials/historical/rituxan.jsp (last visited March 21, 2005) and Johnson & Johnson SEC Form 10-K for 2005 at p. 30 (reporting sales for product Remicade), found at http://www.shareholder.com/Common/Edgar/200406/950123-05-3140/05-00.pdf (last visited, March 21, 2005)..

[8] *See Monoclonal Antibodies with Clinical Indications*, *at* http://imgt.cines.fr/textes/IMGTrepertoire/GenesClinical/ (last visited March 21, 2005)(index page to lists of monoclonal antibodies).

[9] Data Monitor, *Therapeutic Antibodies: Capitalizing on the Fully Human Wave*, at 5 (Nov. 2003).

[10] Fed. Trade Comm'n, *supra* note 2, ch. 3, at 19.

antibody binding or therapeutic characteristics.[11] The importance of these tools is clear. Between 1980 and 2000, a study of 186 monoclonal antibodies which entered clinical trials showed that only 3% of all mouse monoclonal antibodies were approved by the FDA, while 25% of humanized monoclonal antibodies were approved.[12] Importantly, the research tools used in the identification, characterization and optimization of therapeutic antibodies have minimal to no use outside of the development of new drugs.

B. If Research Tools Are Not Protected by Patents, There Would Be Substantial Risk That Such Tools Will Not Be Developed In The Future

The tools to identify, characterize, and optimize monoclonal antibodies have primarily been discovered and developed by academic institutions and small to mid-size biotechnology companies. Frequently, researchers who originally discover a highly technical research tool at academic institutions form companies in order to obtain sufficient funding to fully develop the technology. That route was taken by Vaccinex. Not unexpectedly, the majority of these tools are the subject of one or more patents. These "tool companies," just as much as drug development companies, have relied on their patents to obtain the necessary capital to develop and commercialize their tools.

Enforceable patents covering research tools are imperative to the existence of small and mid-sized companies in the biotechnology industry, such as those developing tools necessary for the discovery of new

[11] *See, e.g.*, Janice M. Reichert, *Monoclonal Antibodies in the Clinic*, 19 Nature Biotechnology 819, 819 (2001).
[12] *Id.*

therapeutic monoclonal antibodies. In the early stages, these companies are funded primarily by venture capital, money from industrial partners arising out of collaborations, and a small amount of federal money. Once these complex technologies develop beyond the most rudimentary levels, however, there is insufficient public sector funding to fully develop these tools. Therefore, the very existence of these technologies depends largely upon private funding.

A recent study shows that as much as 80-90% of private funding of biotechnology firms has been venture capital since the mid 1990s.[13] Most every firm needs to go through the process of raising capital multiple times and the amount of money raised, to a large degree, determines the speed they are able to develop their technologies and enter into external collaborations. Patents are essential to raising this capital. As one panelist before the Federal Trade Commission testified, "patent protection will be critical in encouraging investment in the next generation of research tools, which might reduce the costs and time required for the clinical trial phases, which are the most 'expensive part' of the drug development process."[14]

Private funding is driven by the ability to obtain intellectual property protection. As a general rule, venture capitalists perform thorough due diligence before they invest in the firms. An analysis of the strength of a firm's intellectual property is a critical part of this due diligence process. In an international study of 115 young biotechnology firms in the United States and Northern

[13] Terry C. Bradford, *Evolving Symbiosis—Venture Capital and Biotechnology*, 21 Nature Biotechnology 983, 98X (2003).
[14] Fed. Trade Comm'n, *supra* note 2, ch. 3, at 20.

Europe, the author noted strong links between acquired capital and the number of patents held by these companies.[15]

C. Patents on Research Tools Do Not Block New Drug Development Because Patentees Will License Their Patents To Receive A Return On Their Substantial Investments

Some of the briefs before the Court argue that a broad interpretation of the safe harbor exemption is essential for developing new drugs for the public's ultimate benefit. The argument is flawed. Merck argues that

> [i]f the Court of Appeals' opinion is upheld, the patent laws would allow the holder of a patent . . . to enjoin a medical researcher from conducting studies . . . that could yield ground-breaking cures for people.

(Pet. Br. at 4.) While this scenario is permitted under the Patent Act, it is simply not an option for the holders of most research tool patents;

> [t]he patent holder intends to make money from [the patent's] utilization. If he refuses to deal in any individual case, that would not increase his political power or give him additional claims to public revenue. Refusing to deal is a loss of opportunity.[16]

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[15] Lillian Waagø, *Factors Related to Capital Acquisition in Young Biotechnology Firms* 14 (May 2004), *at* http://web.bi.no/forskning/ncsb2004.nsf/pages/index (last visited March 21, 2005).

[16] Richard A. Epstein & Bruce N. Kuhlik, *Is There a Biomedical Anticommons?*, Regulation, Summer 2004, at 54, 55, *available at* http://cato.org/pubs/regulation/regv27n2/v27n2-7.pdf (last visited March 21, 2005).

While biotechnology "tool companies," including Vaccinex, often have an ultimate goal of developing and marketing drug products themselves, they lack, at least at the early stages, the resources, manpower and capital to fully exploit their tool technology. For example, where a small to mid-size biotechnology company might have sufficient resources to complete basic and preclinical research on a small number of therapeutic antibodies, they are unlikely to have the resources necessary to take the antibody into clinical studies. Accordingly, early revenue generation is a very attractive prospect for these companies. Thus these companies have every incentive to partner with other biotechnology companies or pharmaceutical companies, for use of the patented tools in areas outside the specific indications the company is interested in. If patentees blocked others from using their platform tool technology by refusing to grant licenses, they would only be hurting themselves.

Furthermore, tools used for drug development are very often "non-rival" in nature and can be used by several entities that are not in direct competition with one another. This situation is especially true with tools for making therapeutic antibodies. For example, a tool for humanizing an antibody is broadly applicable and can be used to humanize potentially therapeutic antibodies regardless of the antibody's target. The "non-rival" nature of such research tools greatly enhances the incentive of the owner of a patented tool to widely grant licenses under reasonable terms. Accordingly, "tool companies" whose technology platform revolves around the identification, characterization, and/or optimization of monoclonal antibodies, routinely form alliances with, and/or license their tools to, larger companies with more extensive drug development capabilities.[17]

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[17] *See, e.g.*, *The Big Business of Antibody Therapeutics: Pipeline & Evolving Strategies*, 16 Drug & Market Dev. 803, 808 (2005).

Given the ability of smaller "tool companies" to fully develop their tool technologies through private funding and partnerships, larger companies have a broad selection of research tools available to them through licensing or collaborative partnerships, and a competitive marketplace is formed. The larger companies can choose the most appropriate tools based on sound scientific and economic considerations. Thus, research tool patents foster drug development by ensuring that there are proper incentives for such biotech companies to be formed for the purpose of commercializing their tools. Absent such incentives, there may be fewer innovative tools for drug developers to choose from, because the research would not be fully developed based on public funding alone.

II. The Trial Court and the Court of Appeals Correctly Concluded that the Evidence Supported the Jury's Finding that the Patented Invention Was Not Solely Used In Research That Was Reasonably Related to Developing Information for Submission to the FDA

It is indisputable that the NCI IND application was not part of the record before the Court of Appeals. Since Merck admitted that not all of the challenged activities came within the safe harbor provision and since there was more than sufficient evidence to support the jury's specific finding that the exemption did not cover all of Merck's activities, Merck's JMOL was properly denied and the Court of Appeals properly affirmed that decision.[18]

[18] The error in the jury's damage award was cured by the proceedings on remand from the Court of Appeals.

A. The Exemption Extends Only to Infringing Activities That are "Solely For Uses Reasonably Related to the Development and Submission of Information" to the FDA

Merck's arguments here for a broader construction of the safe harbor exemption emphasize the "reasonably related" language of the provision and minimize the significance of "solely." The inclusion of both modifiers is critical to maintaining the balance Congress intended. That balance cannot be struck in favor of exempting activities that produce data that ***might*** subsequently be used as part of an IND application. The focus required by the statute is whether the infringement — at the time it occurred — was an activity that "solely" and "reasonably" related to development and submission of information to the FDA. The trial court's instruction captured this balance:

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

(J.A. at 57a.)

That instruction tracked Merck's requested instruction closely.[19] It in fact defined the exemption more broadly than the statute requires because it substituted the words "relatively directly" for the statutory language of "solely for uses reasonably related" to the generation of FDA information. While Merck challenged the district court's denial of its JMOL, it did not challenge the jury instructions in its appeal to the Federal Circuit.

B. The Evidence Supported the Jury's Specific Finding That Merck's Activities Did Not Come Within Merck's Own Definition of the Exemption

Judge Fitzgerald reviewed the evidence and denied Merck's JMOL because he concluded that, "[c]onsidered as a whole, the evidence is sufficient to establish that . . . any connection between the infringing Scripps experiments and FDA review was insufficiently direct to qualify for the exemption." (P.A. at 50a.) Judge Fitzgerald cited several specific parts of the evidence that supported the jury's verdict. The verdict form carefully walked the jury through the applicable legal analysis and required them to focus specifically on the FDA exemption. (J.A. at 58a.)

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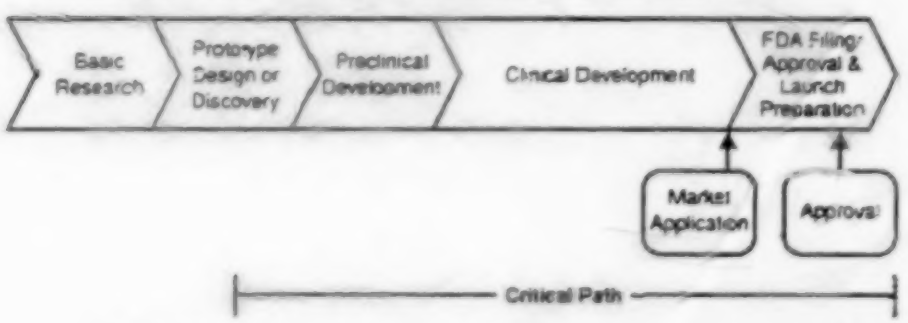
[19] Merck requested the following instruction from the trial court: "For certain of the accused activities, the defendants contend that they do not infringe or induce the infringement of the asserted patent claims based upon a statutory exemption known as the Food and Drug Administration or "FDA" exemption. To prevail on this defense any particular allegedly infringing activity, *[sic]* the defendants must prove by a preponderance of the evidence that it would be reasonable for a party in the defendants' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve a new drug product." (Docket # 930, Ex. G1 (editorial marks and stricken text omitted))

Merck does not focus on the sufficiency of the evidence to support the jury verdict under the instructions that were given. Merck instead seeks a legal ruling based on a construction of the exemption far broader than the one it requested at trial. Merck in effect now seeks to change the words "relatively directly" to "then or in the future." The new version stretches the language of the statute beyond the limits Congress intended.

C. Merck's Position Sweeps Activities that are Not Solely and Reasonably Related to FDA Information Within the Exemption

Merck's brief includes a depiction of the timeline for development of new drugs:

Figure 4: The Critical Path for Medical Product Development



Merck's discussion of the exemption (Pet. Br. 36-41) suggests that every activity on the "Critical Path," the entire "Prototype Design or Discovery" phase and perhaps some aspects of the "Basic Research" phase are covered by the safe harbor exemption. That position, we submit sweeps far too broadly and includes many uses of patented research tools that should not be included in a proper construction of the statute.

None of the activities in the basic research phase can be "solely" uses for developing information for submission to the FDA. Merck seems to agree with this view, except that it

seems to limit non-exempt basic research to "university scientist[s]," implying that if the research is done in a commercial laboratory there is a sufficient connection to a potential FDA application. (Pet. Br. at 38-39.)

Merck argues that "[e]verything changes when a researcher endures the . . . process of screening untested structures . . . ." (Pet. Br. at 39.) That argument seeks an exemption for activities that plainly are not "solely" and "reasonably" connected to FDA information. Screening activities are primarily designed to identify promising candidates for FDA applications. Those activities may, on occasion, generate some relevant FDA material for the specific compounds that are identified as promising candidates, but the vast majority of the screened compounds are rejected as unsuitable. It is, therefore, impossible to conclude that the screening phase is "solely" used to develop FDA information.

Research tools enable the discovery of drugs whose existence cannot be assumed or predicted and their use is not, therefore, directly or relatively directly and certainly not "solely" related to development or submission of information to the FDA. The key outcome of using a research tool is the discovery that an effective drug might exist. After further research, initiation of an FDA application might be warranted. There is no identifiable FDA process for which information needs to be developed prior to the realization that a FDA application might be warranted. The use of the research tool in screening candidates cannot be "solely" related to submission of information to the FDA since it cannot be known at the time the tool is employed whether any information will ever be submitted to the FDA

We believe that virtually all of the activities in the Basic Research and the Prototype Design or Discovery phases are outside the scope of the exemption. Certainly any "prototype discovery" is a process of identification, not

experimentation on an already discovered compound that is about to proceed through the FDA process. Similarly, "prototype design" includes the characterization of those compounds identified, and optimization of identified compounds which may have promising characteristics, but insufficient potential. As in the "screening" stage, many and perhaps all of the candidates, after characterization and optimization attempts, will be rejected as unsuitable. Much, if not most, of the "prototype design" phase is also likely to be undertaken for multiple uses and not solely for generating FDA information.

D. The Court of Appeals Did Not Embrace a Clinical/Preclinical "Bright Line" Principle

This case has been presented to the Court as one where the Court of Appeals for the Federal Circuit held that the exemption "covers only the final stage in the FDA approval process" — the clinical research stage. (Pet. Br. at 4.) That description distorts what the Court of Appeals held and is based on isolated phrases from the court's opinion taken out of context.

The crux of the Court of Appeals' decision was the majority's unequivocal conclusion that the challenged "experiments did not supply information for submission to the . . . FDA." (P.A. at 11a.) That conclusion was necessarily based on the record which did not include the IND application that is used by Merck and the Solicitor General to argue that some of the preclinical experimental data was in fact submitted to the FDA. The Court of Appeals did not draw a line between IND applications and NDA/ANDA filings. Similarly that court did not draw a line between clinical and preclinical phases of research. The opinion may not have been as clear and precise about the record as it should — in hindsight — have been, but

deficiencies in explaining the result should not lead to a reversal of the judgment.

E. Most Uses of Patented Research Tools Will Fall Outside the Exemption, But Some May Well Be Exempt

We do not argue for a "bright line" test that puts all uses of patented research tools outside the exemption. The focus should not be on what the patented invention *is* but on how it is *used* in the challenged activities. The nature of research tools will, most often, lead the fact-finder to conclude that they have not been used "solely" as part of an activity that is "reasonably" related to the development or submission of FDA information. But there are likely to be some cases where a promising candidate has been identified through use of a patented research tool, a decision to seek FDA approval has been made, and it is then necessary to use the patented invention solely to gather information for submission to the FDA. When the invention is used in that final post-identification, pre-submission stage, it would be within the scope of the exemption.

Conclusion

For the reasons stated, the Court should either affirm the decision of the Court of Appeals based on the record that was before that court or dismiss the writ as improvidently granted.

Respectfully submitted,

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March 22, 2005